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REVIEW ARTICLE

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Using pharmacokinetics for tailoring prophylaxis in people with hemophilia switching between clotting factor products: A scoping review

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Abstract

The objective of this scoping review is to summarize the current use of pharmacokinetics for tailoring prophylaxis in hemophilia patients switching between clotting factor products. Patients with hemophilia may require switching of clotting factor concentrates due to a variety of factors, but there have been perceived risks associated with switching, such as inhibitor development or suboptimal protection due to inadequate dosing while titrating treatment. Studies that look at patients switching from one clotting factor concentrate to another are categorized in terms of their primary and/or secondary objectives, notably biosimilarity and comparative pharmacokinetic studies and inhibitor development studies. Research on how best to switch concentrates with respect to dosing regimen are lacking, and currently a trial-and-error approach is used for dosing the new factor concentrate. In the future, studies looking at the predictability of pharmacokinetics (PK) of a new factor concentrate based on individual PK knowledge of the original factor concentrate may offer clinical benefit by providing a safer switching approach and protocol.

KEYWORDS

drug substitution, factor IX, factor VIII, hemophilia A, hemophilia B

Essentials

- We assessed use of pharmacokinetics (PK) to tailor hemophilia prophylaxis when switching factor products.
- Identified studies primarily assessed biosimilarity and none used PK to inform switching.
- Switching is common based on a review of the WAPPS database for both factor VIII and IX.
- Evidence-based switching methods (eg, population PK) may improve dosing during switching.

1 | INTRODUCTION

The mainstay treatment of hemophilia involves administration of factor concentrates. In the past, factors VIII (FVIII) and IX (FIX) infusions were given during or soon after an acute bleed. This "on-demand" treatment decreased the number of patients with joint deformities but also significantly lowered their morbidity and mortality, ultimately increasing their quality of life.[1] This practice was soon to be

*Listed in the appendix.

found suboptimal and a study by Aledort et al demonstrated that severe hemophilia patients without inhibitors undergoing an on-demand treatment regimen still experienced reduced orthopedic outcomes and increased deteriorated joints compared to those treated prophylactically.[1,2] Prophylactic FVIII or FIX infusion has now been accepted as the standard for treating hemophilia patients well before joint damage is apparent.[2–6]

Prophylaxis was conceived as repeatedly dosing the patient so as to obtain a measurable factor activity at all times. The challenge is that appropriate dosing regimens vary by patient and factor concentrate and should be individualized from a therapeutic and economic standpoint.[6–8] A "trial-and-error" approach is usually adopted, which involves using a typical prophylactic dosing regimen of 20 to 50 IU/kg, a dose that should provide the average patient with hemophilia with enough clotting factor to achieve the goal of a trough activity ≥0.01 IU/mL at 48 hours. However, this trial-and-error approach fails to account for individual pharmacokinetic (PK) variability and, as per Iorio et al,[9] may lead to suboptimal results.

The trial-and-error approach is used again when switching between factor concentrates. Common practice in this scenario is that either the dose is initially kept the same as before the switch and frequency is adjusted proportionally to the relative expected change in terminal half-life, or the dose and frequency tested in the pivotal studies are used in a first instance. Current guidelines suggest initiating extended half-life (EHL) products at the same dose as standard half-life concentrates but reducing the infusion frequency from 3 to 2 times weekly, and subsequently adjusting the dose based on a population pharmacokinetic (PopPK) approach.[10,11] When a person with hemophilia switches between factor concentrates, the person is switching from a product with known PK, or at least with known outcomes (eg, dose required to reduce bleeding events), to one with unknown PK. Dosing a factor concentrate with unknown PK introduces the risk of underdosing or resource wastage, leading to increased risk of bleeds or unnecessary use of factor concentrate, respectively.

The decision to switch between factor concentrates depends on a variety of factors, and shared decision making while assessing the product's safety, efficacy, cost, and convenience is essential before introducing a new product. The availability of newer and safer FVIII concentrates has resulted in switching between different plasma-derived or recombinant FVIII concentrates throughout the course of hemophilia treatment.[12] Newer FVIII products report to have better PK in terms of longer half-life and thus may provide the advantage of fewer infusions.[12] Other reasons for switching FVIII products may include cost savings, via a tender-based national plan coverage or otherwise, side effects, drug shortages, or hypersensitivity to the formulation.[12]

The optimal approach to dose selection when switching between factor concentrates remains unknown. To answer the question of what is known about the current use of PK for tailoring prophylaxis in people with hemophilia switching between factor concentrates, we conducted (1) a scoping literature review, searching for empirical evidence regarding optimal switching practice; and (2) a review of the Web-Accessible Population Pharmacokinetics Service–Hemophilia (WAPPS-Hemo) database available to explore the practice of switching as recorded in the real world. WAPPS-Hemo is a globally accessible online tool allowing hemophilia treaters to estimate individual PK using a population PK approach based on a limited set of 2 to 3 plasma factor activity measurements and patient covariates (eg, age, weight, height). Patient covariates and PK profiles gathered by WAPPS-Hemo are deidentified and stored in a database. This database is available for research purposes to the members of the WAPPS-Hemo research network.[13] The WAPPS-Hemo database provides information on current practices regarding product switching, as patients who have had >1 infusion recorded and have used >1 factor concentrate can be tracked within the system.

2 | METHODS

2.1 | Scoping review

The scoping review process followed these steps: (1) identify possible eligible studies; (2) select relevant studies; (3) chart the data; and (4) collate, summarize, and report the results, as proposed by Arksey and O'Malley.[14] Following the PCC mnemonic,[15] studies included hemophilia A or B patients (Population) switching between different factor concentrates and including appropriate PK assessments (Concept) and without any limitation as to reasons for switching, socioeconomic setting, and underlying health care system characteristics (Context). Relevant studies were prospective in nature. A search strategy was developed using medical subject headings (MeSH). The literature search was independently performed in PUBMED (MEDLINE) in September 2018 by both JKY and ANE. Search terms included:

- ("Hemophilia A"[MeSH] OR "Hemophilia B"[MeSH] OR "Factor IX"[MeSH] OR "Factor VIII"[MeSH]) AND switch*
- ("Hemophilia A"[MeSH] OR "Hemophilia B"[MeSH]) AND "Cross-Over Studies"[MeSH]
- ("Hemophilia A"[MeSH] OR "Hemophilia B"[MeSH]) AND "Pharmacokinetics"
- ("Hemophilia A"[MeSH] OR "Hemophilia B"[MeSH]) AND "Bioequivalence"

2.2 | WAPPS data review

For this review, all patients within the WAPPS-Hemo database were eligible for inclusion unless they had only 1 infusion or had only 1 type of factor concentrate recorded on multiple occasions (Figure 1). The WAPPS user agreement allows reuse of the data for modeling and other research purposes, as described in the WAPPS study protocols, approved by the ethics boards at McMaster University and the University of Waterloo and registered in clinicaltrial.gov (NCT02061072, NCT03533504).

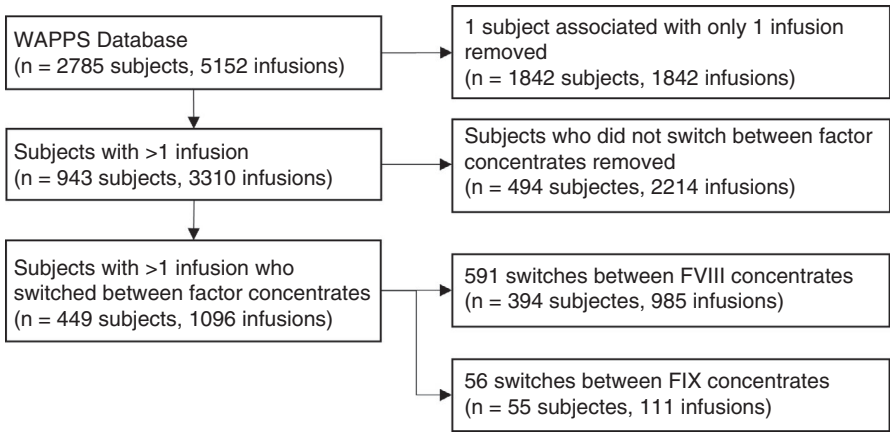

FIGURE 1 Study flow diagram of WAPPS data

3 | RESULTS

3.1 | Study selection

There were no research articles that specifically addressed the optimal approach to switching between factor concentrates. However, there were 39 peer-reviewed scientific articles that fell within our inclusion criteria (Figure 2). Reviewer 1 identified 39 and reviewer 2 identified 38 that were identical to those selected by reviewer 1. Upon discussion of the missing article, the reviewers decided to include it as it met the inclusion criteria. The 39 articles were the only studies that could provide treaters with methods for evidence-based switching using PK and were thus sorted based on their primary objective and appraised. Studies included bioequivalence or comparative PK studies, as well as inhibitor development studies during switching. All 39 studies are outlined in Table 1 (FVIII) and Table 2 (FIX).

3.2 | Biosimilarity/bioequivalence or comparative PK studies

Strictly speaking, the term *bioequivalence* should not be used for drugs produced by biotechnology; the term *biosimilarity* is more appropriate.[16] However, bioequivalence was the terminology used in many of the studies as many were published prior to the 2014 European Medicines Agency's guidance.[16] Irrespective of the term used, studies assessing biosimilarity/bioequivalence did not usually enhance a switching protocol as a primary objective; however, their standardized dosing protocol allowed for comparison of individual PK profiles between the 2 brands under study. Thus, this section focuses on biosimilarity and comparative PK studies as both types compared population PK.

There were a limited number of studies that were biosimilarity or comparative PK studies (n = 34) (Tables 1 and 2). Biosimilarity refers to a lack of statistically significant differences in drug exposure between 2 drug products. In multiple crossover studies, biosimilarity was assessed by using a PK analysis to derive the maximum plasma factor activity (C_{max}) following infusion and the area under the plasma concentration vs. time curve (AUC).[17–19] To establish biosimilarity, the ratio of the logarithmic geometric mean values of C_{max} and AUC must fall within the interval of 80% to 125% based on a 90% confidence interval.[17,18]

All of the studies looking at comparing PK between 2 brands used PK end points, as suggested by the International Society of Thrombosis and Haemostasis and American and European regulatory bodies.[12–14] The test dose before and after the switch was almost always identical, usually with a weight-based dosing of 50 IU/kg of the factor concentrates. Using the same dose for different concentrates is a requisite for biosimilarity studies. All trials studied included a washout period of between 2 and 7 days before starting the trial and between different factor concentrates (Tables 1 and 2).

Biosimilarity/bioequivalence testing employs various types of statistics that are dependent upon the trial design. Most trial designs for biosimilarity testing of clotting factors employed a

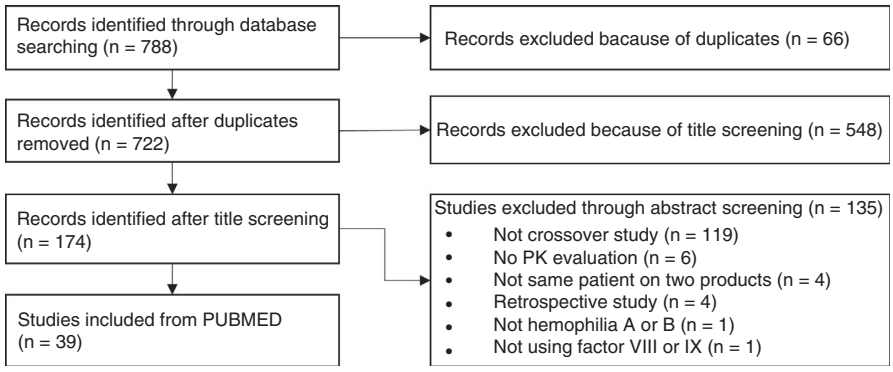

FIGURE 2 Study flow diagram of PUBMED search

TABLE 1 Summary of studies of hemophilia patients switching between factor VIII concentrates

Author	Products	Dose (IU/kg)	No. of subjects screened for PK	Age range (mean) [median]	Minimum washout period (d)	Primary objective
Biosimilarity or comparative PK studies						
Di Paola[17]	(1) Advate (2) ReFacto	50 ± 5	21	19-72 (35.8) [30]	3	Compare PK of ReFacto and Advate to establish bioequivalence
Dmoszynska[31]	(1) Prior FVIII product (2) Optivate	50	15	12-65	3	Investigate the PK of Optivate against other FVIII products
Fijnvandraat[32]	(1) rFVIII SQ (2) Octonativ M	50	12	17-64 (34)	4	Compare PK of rFVIII SQ and Octonativ M
Kessler[18]	(1) ReFacto (2 formulations) (2) Hemofil M	50	19	18-44 (26.3)	5	Compare PK of the 2 formulations of ReFacto with Hemofil M to establish bioequivalence
Klamroth[23]	(1) Advate (2) rFVIII single-chain	50	27	19-60 (35.4)	4	Compare PK parameters of rFVIII single-chain with full-length rFVIII
Martinowitz[22]	(1) Advate (2) N8	50	25	13-54 (24)	4	Compare PK profiles of N8 and Advate to establish bioequivalence
Morfini[33]	(1) pdFVIII (2) rFVIII	25-56 25-45	17	15-51 (27.7) [24.9]	7	Compare PK profiles of 2 different classes of FVIII concentrates
Morfini[34]	(1) Recombinate (2) Hemofil M	50	47	6-62 (26.4)	7	Compare PK profiles of Recombinate and Hemofil M
Morfini[35]	(1) Hemofil M (2) Monoclate HT (3) Monoclate P	25	10	-	7	Compare in vivo behavior among the 3 products
Recht[36]	(1) Advate (2) Xyntha	50	24	12-60 [24]	3	Demonstrate PK equivalence of Advate
Shah[19]	(1) Advate (2) Kovaltry	50	18	19-64 (37.3) [36]	3	Compare PK profile of Advate and Kovaltry
Shirahata[37]	(1) BAY14-2222 (2) Kogenate	50	5	15-43 (32) [35]	5	Compare PK profile of BAY14-2222 and Kogenate
Biosimilarity or comparative PK and inhibitor development studies						
Abshire[38]	(1) Kogenate (2) rFVIII-FS	50	35	-	4	Compare PK and safety of Kogenate and rFVIII-FS
Coyle[39]	(1) rFVIII-FS (2) BAY 94-9027	25/50 25/60	14	21-58 (36.1)	3	Assess PK and safety of BAY 94-9027
Kulkarni[40]	(1) Prior FVIII product (2) Turoctocog alfa	- 25-60	69	1-11 (6.1)	3	Investigate safety, efficacy, and PK properties of turoctocog alfa
Mahlangu[29]	(1) Advate (2) rFVIIIFc	50	30	12-65 [29]	-	Evaluate safety, efficacy, and PK of rFVIIIFc
Meunier[41]	(1) Prior FVIII product (2) N8-GP	- 60	24	0-11 (6.0)	-	Assess safety, efficacy, and PK of N8-GP
Mullins[42]	(1) Advate (2) BAX855	60 ± 5	31	1-11 (6) [6]	-	Determine immunogenicity, PK, efficacy, safety, and quality of life using BAX855

(Continues)

TABLE 1 (Continued)

Author	Products	Dose (IU/kg)	No. of subjects screened for PK	Age range (mean) [median]	Minimum washout period (d)	Primary objective
Powell[43]	(1) Kogenate (2) Kogenate with pegylated liposome carrier (13 or 22 mg/kg)	35	26	12-60	2	Investigate the safety, tolerability, bioavailability, pharmacokinetics, and pharmacodynamics of Kogenate with pegylated liposome barrier compared with standard Kogenate
Schwartz[44]	(1) Koate-HS (2) Recombinant FVIII	50 20-40	17	-	7	Compare PK of plasma-derived and recombinant FVIII, assess efficacy of recombinant FVIII for home therapy, and assess efficacy for major surgical procedures and hemorrhage
Skotnicki[45]	(1) Vocento (2) Biostate-RP	50	17	18-57 (36.5) [37]	4	Evaluate efficacy, safety, and PK of Voncento
Tiede[46]	(1) Prior FVIII product (2) N8-GP	- 25/50/75	26	20-60 [36.5]	4	Evaluate safety and PK of N8-GP in comparison with previous FVIII products
Young[30]	(1) Prior FVIII product (2) rFVIIIFc	50	60	1-11 [5]	3	Evaluate safety, efficacy, and PK of rFVIIIFc
Inhibitor development studies						
Hsu[47]	(1) Kogenate (2) Koate-HS	50 -	12	23-53 (37.8)	7	Evaluate safety and efficacy of Kogenate
Powell[48]	(1) Advate (2) rFVIIIFc	25/65 25/65	19	23-61 (34.6)	3	Evaluate safety and treatment-emergent adverse events, development of antibodies, and laboratory monitoring

-, not specified; FVIII, factor VIII; pdFVIII, plasma-derived factor VIII; PK, pharmacokinetics; rFVIII, recombinant factor VIII; SQ, subcutaneous.

2 × 2 × 2 crossover design. All biosimilarity and comparative PK studies observed average biosimilarity or average mean PK parameter differences and did not examine individual differences. Average biosimilarity assesses the PK between-subject variability (BSV) but does not directly assess the within-subject variability (WSV) over time. This may be reasonable given the a priori knowledge that clotting factor concentrates demonstrate a high PK BSV and low WSV within 1 brand,[6] and therefore the assessment of individual biosimilarity may not be necessary. Individual biosimilarity assesses for both the mean and variability of PK metrics and also the ratio of the 2 drug products on an individual basis and is recognized when both the average biosimilarity is established and the subject-by-formulation effect is insignificant.[20] Average biosimilarity is important to assess mean PK differences in a population, but individual biosimilarity is highly impactful if the goal is to give prescribers confidence that biosimilarity will occur when a patient on one of the drug products is switched to the other.

In order for a drug to be therapeutically equivalent to another product, it requires the same active pharmaceutical ingredient (API), dosage form, strength, route of administration, and established bioequivalence.[21] Because clotting factors are not identical, as they are biologics, the PK BSV and WSV of the 2 brands may not hold; this is not the case with small molecules, where the API systemic disposition is exactly the same between 2 drug products. As a result, the individual concentration-time profile of 1 factor concentrate can be different as compared to another factor concentrate of the same dose and frequency. If individual biosimilarity for 2 factor concentrates is established, they can be used interchangeably, and the PK of one factor concentrate is therefore predictive of the other. However, no study confirming individual patient biosimilarity has been completed because it is difficult to achieve. In a study by Di Paola et al,[17] patients who switched from Advate to ReFacto had very different individual PK parameters even though the average PK parameters were similar. Similar findings were observed with Martinowitz et al[22] and Klamroth et al (Figure 3).[23] The conclusion that 2 factor concentrates are bioequivalent does not mean that individuals will achieve the same concentration-time profile if the same dose is given. Likewise, similar average half-life between 2 factor concentrates does not mean that the half-life between 2 factor concentrates in any given individual will be similar; some individuals in Figure 3 had drastic differences in their PK across factor concentrates.

TABLE 2 Summary of studies of hemophilia patients switching between factor IX concentrates

Author	Products	Dose (IU/kg)	No. of subjects screened for PK	Age range (mean) [median]	Minimum washout period (d)	Primary objective
Biosimilarity or comparative PK studies						
Alamelu[49]	(1) Alphanine (2) Benefix	50	9	15-73 (41.2) [42]	7	Compare PK and pharmacodynamics properties of rFIX and pdFIX
Aznar[50]	(1) Immunine/ Octanine (2) FIX Grifols	65-75	25	12-38 (23.1)	7	Compare pharmacokinetic profile of FIX Grifols to available Immunine or Octanine
Ewenstein[51]	(1) Benefix (2) Mononine	50	43	7-75 [18.5]	7	Assess PK properties of the 2 products and address how variables affect in vivo recovery and half-life
Goudemand[52]	(1) FIX-SD-15 (2) FIX-SD	60	11	-	10	Compare PK and coagulation activation markers of FIX-SD-15 and FIX-SD
Liebman[53]	(1) Alphanine (2) Mononine	40	12	-	7	Evaluate kinetics of FIX activity and protein
Lissitchkov[54]	(1) Benefix (2) Alphanine	65-75	22	15-45 (27)	7	Compare PK between Benefix and Alphanine
Martinowitz[55]	(1) Benefix (2) IB1001	75 ± 5	32	15-64	5	Compare PK of IB1001 with those of Benefix and assess consistency of PK parameters
Thomas[56]	(1) Conventional FIX (2) High-purity FIX	75	19	-	7	Compare PK of high-purity FIX to conventional FIX
Windyga[57]	(1) Benefix (2) BAX326	75 ± 5	86	12-65	5	Characterize PK profile of BAX326 and determine PK equivalence with Benefix
Biosimilarity or comparative PK and inhibitor development studies						
Collins[58]	(1) Benefix (2) IB1001	75 ± 5	32	14.8-64.5 (32.7) [29.9]	5	Establish PK noninferiority of IB1001 to Benefix, safety, and efficacy
Kenet[59]	(1) Prior FIX product (2) rFIX-FP	50	27	1-11 (5.9)	-	Evaluate PK, efficacy, and safety of rFIX-FP
Inhibitor development studies						
Negrier[60]	(1) Prior FIX product (2) N9-GP	- 25/50/100	20	21-55 [30]	7	Determine safety by evaluating adverse events, antibody formation against FIX and N9-GP, physical examination, and clinical laboratory assessments
Powell[61]	(1) Benefix (2) rFIXFc	50	22	-	5	Determine annualized bleeding rate and development of inhibitors
Solano Trujillo[62]	(1) Immunine (2) BAX326	20-40 75 ± 5	44	1-55	-	Document exposure to Immunine and monitor for inhibitor development

-, not specified; FIX, factor IX; FVIII, factor VIII; pdFX, plasma-derived factor X; PK, pharmacokinetics; rFIX, recombinant factor X.

No study involving switching between factor concentrates where PK was assessed used this information to predict a proper dosing regimen.

3.3 | Inhibitor development studies

The second type of study included patients serially taking at least 2 clotting factor concentrates and had the objective of examining inhibitor development. Inhibitors are antibodies that neutralize clotting factors. These inhibitors are generally measured using the Nijmegen modification of the Bethesda assay.[24,25] Once inhibitors develop in a patient with hemophilia, it becomes much more difficult to treat them, resulting in an increase in morbidity and mortality in the affected population.[24,26]

Eighteen articles were identified in which their primary outcome was focusing on inhibitor development after switching

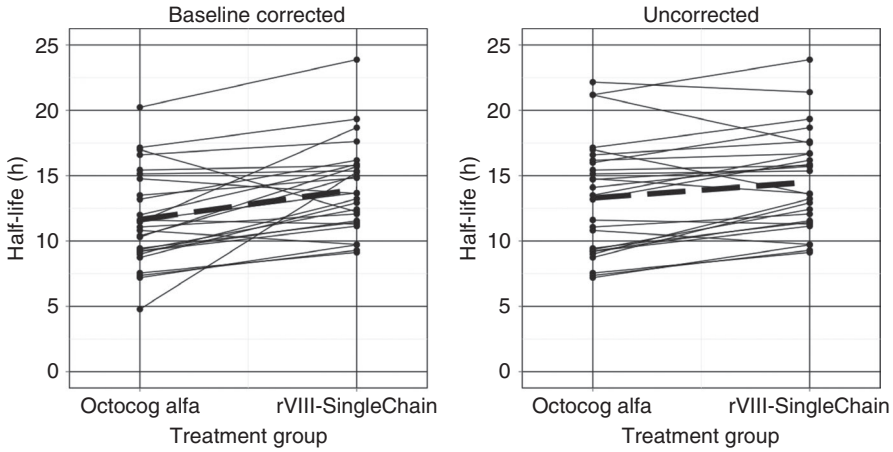

FIGURE 3 Example of individual PK parameters after switching

factor concentrate products (Tables 1 and 2). It was previously thought that switching between factor concentrates was associated with an increased risk of inhibitor development,[27] but recent studies have not shown consistent results.[27,28] Although PK data may have been used in their statistical analysis, dosing regimens of each factor concentrate were not tailored based on PK. It was unclear whether the dose provided to the patient after switching was the optimal dosing regimen. Without knowledge of the dosing regimen in patients with hemophilia, it was also unclear whether the overdosing or underdosing of factor concentrate had an effect on inhibitor risk.

No inhibitor study that incorporated PK into its assessment was usable to inform methods for PK-tailored dosing.

3.4 | WAPPS-Hemo data

As of September 15, 2018, there were >250 centers enrolled worldwide with >3000 patients and >6300 infusions recorded. Infusion data was gathered for the purposes of determining the incidence of switching between factor concentrates.

A total of 2785 patients were taken from the WAPPS data platform. The methodology is presented in Figure 1. Of the 2785 subjects, 449 (16%) had infusions on ≥2 concentrates, with a total of 647 switches. A summary of patient demographics is presented in Table 3.

In terms of FVIII products, there were a total of 394 patients and 591 switches, accounting for 91% of total switches on WAPPS-Hemo.

TABLE 3 Demographics from WAPPS patients who have switched between factor concentrates

Parameter	Whole cohort	FVIII	FIX
Subjects (n)	449	394	55
Switches (n)	647	591	56
Age (y)	1-78	1-78	2-68
Body weight (kg)	10-150	10-150	13-117

As of September 2018.

FVIII, factor VIII; FIX, factor IX; WAPPS, Web-Accessible Population Pharmacokinetics Service.

FVIII products, classified based on their molecular structure, are presented in Table 4. Of the 591 switches, the majority of the switches (n = 293) occurred from second- and third-generation recombinant full-length products (50%). There were 208 switches (35%) to EHL products, 73 switches (12%) to B-domain–deleted products, 229 switches (39%) to another recombinant full-length product, and 81 switches (14%) to plasma-derived products.

In terms of FIX products, there were a total of 55 patients and 56 switches, accounting for 9% of total switches on WAPPS-Hemo. FIX products, classified based on their molecular structure, are presented in Table 5. Of the 56 switches, the majority of switches in WAPPS-Hemo occurred when switching from any FIX product to a recombinant Fc-fusion protein FIX product (n = 34), accounting for 61% of all FIX switches.

4 | PHARMACOKINETIC TARGETS WHEN SWITCHING

While literature states the average of PK parameters (eg, half-life) when switching between factor concentrates, the range of such PK parameters can be highly variable. A study by Mahlangu et al[29] compared the terminal half-life of the recombinant FVIII Fc fusion protein, Eloctate, with a standard-acting FVIII concentrate (Advate) in a phase 3 study to determine the safety, efficacy, and PK. On average, the half-life of Eloctate was 1.5 times that of Advate at a dose of 50 IU/kg.[29,30] This provides valuable information about the population, although it is clear from the breadth of factor concentrate brands being switched to and from, as identified in the WAPPS-Hemo database, that this type of study cannot be completed for all scenarios. A study by Young et al[30] demonstrated that the individual half-life ratios of FVIII and Eloctate ranged from 0.79 to 2.98. Such high half-life variability within an individual across FVIII products makes the application of the mean population difference irrelevant for use in individual dosing recommendations.

Of particular note was the lack of evidence that standard-acting factor concentrates have shorter half-lives than long-acting factor concentrates at the individual level. In the study by Klamroth et al,[23] the majority of patients had increased half-life when switching from

TABLE 4 Number of hemophilia patients from WAPPS-Hemo switching between FVIII concentrates

FVIII products		Switch to											
		Plasma-derived	Plasma-derived with vWF	First-gen rec. full-length	Second-gen rec. full-length	Third-gen rec. full-length	Second-gen rec. BDD	Third-gen rec. BDD	Fourth-gen rec. BDD	Third-gen EHL rec. BDD-PEGylated	Fourth-gen EHL rec. Fc-Fusion	Third-gen EHL rec. single-chain	Total
Switch from	Plasma-derived	2	8	6	9	2	3	1	0	0	6	0	37
	Plasma-derived with vWF	4	26	6	20	5	2	0	0	2	10	1	76
	First-gen rec. full-length	4	11	0	15	18	7	6	1	0	2	0	64
	Second-gen rec. full-length	5	16	16	24	57	6	2	4	2	56	3	191
	Third-gen rec. full-length	0	0	8	5	6	3	13	4	12	50	1	102
	Second-gen rec. BDD	1	2	5	7	0	0	1	0	0	1	0	17
	Third-gen rec. BDD	0	0	0	0	2	1	5	2	2	19	1	32
	Fourth-gen rec. BDD	0	1	0	0	0	0	0	0	0	4	0	5
	Third-gen EHL rec. BDD-PEGyl	0	0	0	1	3	0	0	0	0	0	0	4
	Fourth-gen EHL rec. Fc-Fusion	0	1	0	4	9	0	6	6	30	0	0	56
	Third-gen EHL rec. single-chain	0	0	0	1	0	0	0	0	1	5	0	7
Total		16	65	41	86	102	22	34	17	49	153	6	591

BDD, B-domain deleted; EHL, extended half-life; FVIII, factor VIII; rec, recombinant; vWF, von Willebrand factor; WAPPS, Web-Accessible Population Pharmacokinetics Service.

TABLE 5 Number of hemophilia patients from WAPPS-Hemo switching between FIX concentrates

FIX products		Switch to					
		Plasma-derived	Recombinant	Recombinant glycoPEGylated	Recombinant Fc-fusion protein	Recombinant albumin fusion protein	Total
Switch from	Plasma-derived	4	1	0	11	1	17
	Recombinant	0	1	1	22	7	31
	Recombinant glycoPEGylated	0	0	0	0	0	0
	Recombinant Fc-fusion protein	1	0	1	0	5	7
	Recombinant albumin fusion protein	0	0	0	1	0	1
Total		5	2	2	34	13	56

FIX, factor IX; WAPPS, Web-Accessible Population Pharmacokinetics Service.

octocog alfa to a recombinant FVIII single-chain concentrate; however, this was not the case for 4 of 27 subjects. The potential risk of assuming an increase in half-life when switching from a standard-acting to a long-acting concentrate may lead to increased risk of bleeds due to underdosing. Without assessing individual PK parameters, the current approach of using population-level information to switch between factor concentrates may not yield expected results.

It would be desirable to estimate dosing regimens across a switch using an individualized approach. In an ideal scenario, where population PK tailored prophylaxis was widely adopted, patients planning on switching to a different factor concentrate would have information regarding their own PK estimates on their current factor concentrate. In theory, combining the knowledge of the individual's PK of a factor concentrate prior to the switch (origin concentrate) with the knowledge of the population PK characteristics of the concentrate after the switch (destination concentrate) may potentially lead to the ability to predict individual PK estimates of the destination concentrate. The accuracy and precision of such an approach have not yet been studied, and empirical demonstration of the feasibility of the process is first required. However, the perspective of enabling better estimation of individual PK on the destination concentrate is undoubtedly appealing. This is an example of a research project that could be performed with the rich WAPPS-Hemo database that contains many hemophilia subjects who have switched between different factor concentrates.

5 | STUDY LIMITATIONS

The volume of literature we expected to find in this specific field was limited. As such, we have not registered the protocol or used the Peer Review of Electronic Search Strategies checklist when conducting our search strategy. We cast a wide net with regards to our search terms, but we are aware that this will limit the internal and external validity of our results.

6 | CONCLUSION

Hemophilia treatment requires accurate and individualized dosing regimens to provide safe, effective, and cost-effective medication use. Although studies looking at bioequivalence/biosimilarity or assessing PK between 2 factor concentrates have led to PK comparisons, these studies lack the information required to predict an optimal dosing regimen for hemophilia patients starting on a new product. Studies that have examined the development of inhibitors did not mention the use of PK parameters to optimize a dosing regimen. As such, there exists no literature on the role or use of PK in optimizing factor concentrate dosing during product switching.

Given these limitations, further research is required to utilize PK parameters from the origin product to predict the PK of the destination product in patients with hemophilia. Due to similarity in PK parameters, especially across FVIII products,[6] dose regimen predictability may be feasible using population PK methods and Bayesian forecasting. For example, standard-acting FVIII concentrates may be compared with other standard-acting FVIII concentrates and, in the same way, with newer long-acting FVIII concentrates.

With the introduction of newer and longer-acting concentrates, the use of PopPK methods will be an integral part in determining and predicting accurate dosing regimens for patients. The use of PopPK can change the current trial-and-error approach into a safer dosing regimen that makes use of prior PK knowledge to ensure patient safety and mindful resource consumption.

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RELATIONSHIP DISCLOSURE

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APPENDIX

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